UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,132	07/07/2006	Sarah Donald	13566.105014	7292

65989 7590 02/11/2008

KING & SPALDING
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-4003

EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	**PAPER NUMBER**
1612	

NOTIFICATION DATE	DELIVERY MODE
02/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,132	DONALD ET AL.	
	Examiner	Art Unit	
	Chris E. Simmons	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *14-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,18 and 19* is/are rejected.

7)☐ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/07/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claim 1 is objected to because of the following informalities: abbreviations should be spelled out at least once in the claims. Accordingly, the claim is objected to for not providing the full definition for "ET-743". Appropriate correction is required.

Claims 14-17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112 – 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 8 provide for the use of a cruciferous indole compound or ET-743, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

For examination purposes, claims 1-8 are not readily identifiable as method claims or product claims. For examination purposes, these claims will be considered as method claims.

Claim Rejections - 35 USC § 112 – 1st Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-4, 6-13, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims recite a composition and methods of use comprising a "cruciferous indole compound". There is insufficient written basis for this limitation in the claims, other than those components explicitly recited and identified in the disclosure.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP 52163. In particular, *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly,* 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5,2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia,* "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.,* 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines,* 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in

general. *Univ. of Rochester v G.D. Searle & Co.*, 249 Supp. 2d 216,225 (W.D.N.Y. 2003).

Applicants have failed to provide any structural characteristics, chemical formula, name(s) or physical properties, aside from the express identification of the indole-3-carbinols found at page 7, third paragraph, that would provide adequate written description of the claimed genus of a cruciferous indole compound. Accordingly, Applicants have not demonstrated that they were actually in possession of, and intended to be used within the context of the present invention, the broad genera of components encompassed by the claims at the time of the present invention.

Claim Rejections - 35 USC § 112 – 1st Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of indole-3-carbinol to counteract hepatotoxicity, does not reasonably provide enablement for 1) cruciferous compounds to counteract side effects, including hepatotoxicity and 2) indole-3-carbinol to counteract side effects other than hepatotoxicity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant claims the use of

cruciferous indole compounds to reduce undesirable side effects inherent in antitumor therapy with ET-743.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

A. State and predictability of the art, and relative skill level:

Although the skill is high in the pharmaceutical art, the hepatoprotective capacity of compounds have proven to be unpredictable as recognized by Applicant in the instant specification at page 5, last paragraph.

B. The breadth of the claims:

The claim is very broad and inclusive of reducing any side effect beyond just

hepatotoxicity caused by ET-743. The claims are further exacerbated by being inclusive of any cruciferous compound even though Applicant suggests the unpredictability of the protective capacity of different compounds at page 5, last paragraph.

C. **The amount of direction or guidance provided and the presence or absence of working examples:**

The specification provides guidance for reducing the hepatotoxicity of ET-743 with indole-3-carbinol. There is no disclosure showing the reduction of other side effects. The disclosure further fails to show the reduction of hepatotoxicity of ET-743 with any other compound other than indole-3-carbinol.

D. **The quantity of experimentation necessary:**

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed cruciferous indole compound could be predictably used reduce the hepatotoxicity of ET-743. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

5. Claims 1-13 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of certain specific tumors

with ET-743 , does not enable the treatment of the vast variety of (cancerous and noncancerous) tumors within the scope of the claims as currently drafted.

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

A. **The nature of the invention, state and predictability of the art, and relative skill level:**

It is unpredictable whether a drug can be used to treat a patient having a cancerous tumor. In the case of cancer, for example, it cannot be predicted if a drug will be successful in treating one type of cancer and this unpredictability increases when trying to treat a broad spectrum of cancers. Although many of the tests are functions related to cancers, these functions are not related to all cancers. Furthermore, even testing functions that are related to particular cancers can be misleading because a controlled environment in vitro cannot predict what will happen in vivo.

The unpredictable nature of cancer assays has long been recognized. See, e.g., Olive Et al. (Clin. Cancer Res. 2006 Sep 15;12(18):5277-87), which provides an overview of the problems involved with predicting the effectiveness of models predictive utility. The predictive utility of a model can only be established in retrospect (last paragraph page 5280). Unfortunately, neither cell-based assays nor xenograft models are particularly successful in predicting drug responses in humans (page 5277, column 2, first full paragraph).

B. **The breadth of the claims:**

The claims are very broad insofar as they recite the treatment of tumors, i.e., a vast array of tumors, including cancers of different types (e.g., breast cancer, colon cancer, etc) and noncancerous tumors. The treatment of the different types of tumors within the scope of the claims has not been demonstrated.

C. **The amount of direction or guidance provided and the presence or absence of working examples:**

The specification provides guidance only for retarding the growth of 13762 tumor cells with ET-743.

D. **The quantity of experimentation necessary:**

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the

instantly claimed composition could be predictably used to carry out the methods inferred by the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

6. Claims 10-13 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of certain specific tumors with indole-3-carbinol, does not enable the treatment of the vast variety of tumors with a vast array of cruciferous indole compounds within the scope of the claims as currently drafted.

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

A. **The nature of the invention, state and predictability of the art, and relative skill level:**

It is unpredictable whether a drug can be used to treat a patient having a cancerous tumor. In the case of cancer, for example, it cannot be predicted if a drug will be successful in treating one type of cancer and this unpredictability increases when trying to treat a broad spectrum of cancers. Although many of the tests are functions related to cancers, these functions are not related to all cancers. Furthermore, even testing functions that are related to particular cancers can be misleading because a controlled environment in vitro cannot predict what will happen in vivo.

The unpredictable nature of cancer assays has long been recognized. See, e.g., Olive Et al. (Clin. Cancer Res. 2006 Sep 15;12(18):5277-87), which provides an overview of the problems involved with predicting the effectiveness of models predictive utility. The predictive utility of a model can only be established in retrospect (last paragraph page 5280). Unfortunately, neither cell-based assays nor xenograft models are particularly successful in predicting drug responses in humans (page 5277, column 2, first full paragraph).

B. **The breadth of the claims:**

The claims are very broad insofar as they recite the treatment of tumors (i.e., a vast array of tumors - cancerous and noncancerous) with a wide variety of different compounds (i.e., cruciferous indole compounds). The treatment of the different types of tumors within the scope of the claims has not been demonstrated. The treatment of

different types of cancers with various compounds within the scope of the claims has not been demonstrated to provide proper enablement.

C. **The amount of direction or guidance provided and the presence or absence of working examples:**

The specification provides guidance only for retarding the growth of 13762 tumor cells with indole-3-carbinol.

D. **The quantity of experimentation necessary:**

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed composition could be predictably used to carry out the methods inferred by the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-13 and 18-19 are rejected under 35 USC 103(a) as being unpatentable over Donald et al. (Cancer Research (2003); 63(18):5902-5908; in Applicant's IDS filed 04/07/2006) in view of US 2004/0108086 A1.

The primary reference discloses yondelis (i.e., ET-743) treatment for cancer may lead to hepatotoxicity. Results suggests that pretreatment with high-dose dexamethasone effectively protects against yondelis-mediated hepatotoxicity (abstract). It discloses indole-3-carbinol, like dexamethasone, has hepatoprotective properties

against damage caused by ET-743, likely by inducing CYP3A (page 5907, second paragraph, about the 6th sentence under *Discussion*). The primary reference does not expressly disclose the indole and ET-743 in the same or separate medicaments.

The secondary reference discloses the use of ET-743 in the preparation of a medicament for an effective treatment of a tumor by combination therapy employing ET-743 with another drug such as dexamethasone, where the ET-743 forms part of the same medicament, or is provided as a separate medicament for administration at the same time or a different time as the drug (See claims). It also discloses that the ET-743 is effective at treating cancers such as melanoma (¶ [0116]).

The secondary reference does not expressly disclose the indole compound and ET-743 in the same medicament.

At the time of the invention it would have been obvious to a person of ordinary skill in the art to incorporate indole-3-carbinol and ET-743 in the same or separate medicaments with the desire to conveniently provide a single administration of both drugs (same medicament) or with the desire to have the flexibility of giving one drug prior to the other (separate medicaments) in order to take advantage of the hepatoprotective properties of indole-3-carbinol against damage caused by ET-743.

Conclusion

No claims are allowed.

The following are pertinent prior art not relied upon for the current office action:

- Shertzer, H.G., Niemi, M.P., Reitman, F.A., Berger, M.L. Byers, B.L. and Tabor, M.W. (1987a). Protection against carbon tetrachloride hepatotoxiclty by pretreatment with indole-3-carbinol. Exptl. Molec. Pathol. 46, 180-189.

- Shertzer, H.G., Tabor, M.W. and Berger, M.L. (1987b). Protection from N-nitrosodimethylamlne mediated liver damage by indole-3-carbinol. Exptl. Molec. Pathol. 4, 211-218.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chris E. Simmons whose telephone number is (571) 272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chris Simmons
Patent Examiner
AU 1612

Frederick Krass
Supervisory Patent Examiner
AU 1614

January 14, 2008